REMARKS

Claims 1, 2, 4-6, 8, 9, 11, 12, 14-23, 25-27 and 29 are pending and under consideration. Claims 1, 2 and 4 have been deleted. Claims 23 and 24 have been amended to correct editorial mistakes. No new matter has been added as a result of these amendments.

Rejection under 35 U.S.C. § 112, First paragraph

(1) Claims 1, 2, 4-6, 8, 15-23, 25-27 and 29 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description.

Applicants respectfully disagree with the Examiner's contention. Applicants submit that existing case law makes clear that the patent disclosures are addressed to persons skilled in the art and that in order to satisfy the written description requirement "one skilled in the art, after reading the original disclosure, must immediately discern the limitation at issue in the claims" (See Purdue Pharma L.P. v. Fauling Inc, 56 USPQ 2d 1481 Fed. Cir. (2000)). It is accepted that the description must clearly allow persons of ordinary skill in the art to recognize that the applicants invented what is claimed. Applicants have amended the claims to limit the subject matter to methods to treat sexual dysfunction using dopamine agonists that are more selective for D4 receptors than for D2 receptors. Applicants have demonstrated that compounds that have higher selectivity for the D4 dopamine receptor over the D2 dopamine receptor (see Table 1) and that are selective agonists of said receptor (see Table A), induce an enhanced sexual response in mammals without inducing the secondary emetic effect (see Tables 3, 4, 6 and 7) Applicants have described the invention using two compounds as examples of compounds that are more than 100 times more selective for the D4 receptor than for the D2 receptor.

The Examiner cites University of Rochester v. G.D. Searle & Co. wherein the court found lack of proper written description. Applicants respectfully state that the reference is not applicable to the application at bar. In said case, the claims were directed to a method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of

PGHS-2. The specification in said case did not disclose any such compound and even less how to achieve the claimed effect. In the present application, Applicants have fully described the claimed effect through two examples of selective D4 agonists, establishing that Applicants had possession of the invention at the time of the filing.

Therefore, Applicants respectfully submit that according to the law, Applicants have shown that Applicants were in possession of the claimed subject matter by an actual reduction to practice of the invention and by describing distinguishing characteristics of the compounds.

(2) Claims 1, 2, 4-6, 8, 15-23, 25-27 and 29 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabled for the compounds that are dopamine D4 agonists, with the exception of the two particular compounds listed in claims 11 and 12. Applicants respectfully disagree. Applicants have provided information to the skilled in the art to produce embodiments similar to those claimed in the application without undue experimentation. Some experimentation will be necessary, but a skilled in the art, without unduly extensive experimentation, will recognize that compounds that act as specific agonists of D4 receptors can be tested for their activity in the sexual behavior of mammals and potential secondary emetic effect.

Applicants have deleted claims 1, 2 and 4, leaving the scope of the claims limited to those compounds that are dopamine receptor agonists with a higher selectivity for D4 receptors over D2 receptors.

In view of the deletion and the foregoing remarks, Applicants respectfully submit the withdrawal of the rejection of claims 1, 2, 4-6, 8, 15-23, 25-27 and 29 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6, 8, 9, 11, 12, 14-23, 25-27 and 29 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Fliri *et al.* WO 99/09025 (hereinafter "WO 99/09025") and Glase *et al.* (IDS, hereinafter "Glase") in view of Fliri *et al.* US Patent No. 5,883,094 (hereinafter '094), and Faraci *et al.*, US Patent No. 5,889,010 (hereinafter '010), and in further view of El-Rashkly *et al.*, US Patent No. 5,779,606 (hereinafter '606).

Specifically, the Examiner maintains the rejection in the previous Office Action. The Examiner additionally provides the following comments.

The Examiner states that Applicants' arguments that '094 and '010 do not teach or suggest the treatment of sexual dysfunction because these references do not provide any working examples for treating sexual dysfunction are not persuasive. According to the Examiner these references teach that dopamine receptors are associated with sexual dysfunctions.

The Examiner further states that Applicants have not explained any proffered data and have not established how any results therein should be taken to be unexpected and significant.

The Examiner further states that a person of ordinary skill in the art would have been motivated to employ D4 receptor agonists such as those disclosed in WO 99/09025 and Glase for treating sexual dysfunction because dopamine receptors are generally known to be related to sexual behavior. The Examiner further states that '606 teaches dopamine agonists particularly known to be useful for treating sexual dysfunction.

Applicants respectfully traverse this rejection for the reasons stated in the previous reply. Those arguments are incorporated herein. Important arguments from the previous reply are reiterated below. Additional comments are also provided herein.

The present invention is directed to a method of treating sexual dysfunction using dopamine agonists selective for the centrally located D4 receptor over D2 receptors; these selective D4 agonists induce an augmented sexual response in mammals without inducing an emetic effect. The prior art in general teaches that the dopamine system may be involved in sexual behavior in mammals. This information comes in great part from the sexual stimulatory side effect observed in Parkinson's patients treated with L-dopa and from the pro-erectile effect of apomorphine (see page 2, lines 10-19 of the present specification). The sexual stimulatory effect is the result of agonists acting on dopamine receptors located in selected areas of the CNS. Applicants are the first to determine that compounds that are selective D4 agonists, i.e. compounds that have a higher selectivity for D4 receptors over D2 receptors, induce an enhancement of the sexual behavior of mammals without inducing an emetic effect. This new and unexpected finding implicates that dopamine agonists that are selective for the D4 dopamine receptor over

the D2 dopamine receptor have a new therapeutic utility in specifically treating sexual dysfunction.

Experiments performed expressly by Applicants demonstrate that: (a) N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole are over 1000 times more selective for D4 rceptors than for D2 receptors (Table 1, page 10 of the present specification); (b) N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole activate D4 receptors therefore are agonists to the D4 receptor (Table A, page 13 of the present specification); (c) N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole induce penile erection in male rats with similar incidence as apomorphine, a known non-selective dopamine agonist (Tables 3 and 4, pages 14 and 15 of the present specification); and (d) N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole unexpectedly induce no emetic effect at doses which induce a sexual response, when compared to apomorphine (Tables 6 and 7, pages 16 and 17 of the present specification).

Through these findings, a method according to the present invention is provided in which selective D4 dopamine agonists are useful for the treatment of sexual dysfunction without the liability of the emetic effect associated with non-selective D4 agonists, like apomorphine for example.

As recognized by the Examiner, WO 99/09025 and Glase do no teach expressly the employment of dopamine D4 agonists for treating sexual dysfunction. The Examiner states that '010 and '094 suggest that D4 dopamine receptor selective compounds may exert a wide range of therapeutical effects, including sexual dysfunctions. The Examiner also includes reference '606, which teaches the use of apomorphine to treat sexual dysfunction.

Applicants' arguments in the previous Reply are incorporated herein. Applicants respectfully submit that the Examiner's motivation to combine the teachings of the cited references employs the improper standard of "obvious to try".

Applicants submit that to satisfy the legal standard under 35 U.S.C. § 103, an Examiner must identify both (i) a suggestion to modify a primary reference in accordance with the teachings of one or more secondary references to achieve the claimed invention and (ii) a reasonable expectation of success in making and using the modified procedure (In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). Furthermore, both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure (In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). The modification must be more than just "obvious to try", which the Court of Appeals for the Federal Circuit has rejected as a standard for obviousness (In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988)). Moreover, in combining references, the Examiner may not use an applicant's disclosure as a guide or template to select elements or features from among prior art references which, when assembled together, arrive at the claimed invention (In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Specifically, '094 teaches that the term "*dopaminergic effective amount*" as used in the specification, "*refers to an amount sufficient to inhibit the binding of dopamine to a dopamine* receptor" (col. 6, lines 21-23). Additionally, the disclosed compounds of the invention "*are useful as dopaminergic agents, i.e. they possess the ability to decrease dopamine mediated neurotransmission in mammals, including humans*" (see columns 10, lines 1-4). Taken as a whole, the description of the compounds disclosed in '094 indicates that the claimed compounds are antagonists, and not agonists like the compounds of the present invention. Therefore, not only this reference does not teach or suggest the use of selective dopamine agonists to treat sexual dysfunction, but also teaches away form the present invention because antagonists will have a totally opposite effect in the sexual behavior of mammals. Reference '094 will have never provided a reasonable expectation of success in using the disclosed compounds to treat sexual dysfunction. Similarly, reference '010 discloses that the term "*dopaminergic effective amount*" as used in the specification, "*refers to an amount sufficient to inhibit the binding of dopamine to a dopamine receptor with the effect of altering (i.e., increasing or decreasing) dopamine mediated neurotransmission*" (Col. 9, lines 55-59). Again, the reference as a whole discloses compounds that may "increase or decrease dopamine mediated neurotransmission", with an indication that the preferred effect is an inhibitory effect in

the binding of dopamine, i.e. antagonists. As with the '094, this reference does not teach or suggest the use of selective dopamine agonists to treat sexual dysfunction, but it actually teaches away form the present invention because antagonists will have a totally opposite effect in the sexual behavior of mammals. With regards to reference '606, the patent claims methods of ameliorating erectile dysfunction and a method for diagnosis the same by sublingual administration of apomorphine, it is known from prioir art that apomorphine is a non-slective dopamine agonist which stimulatory effect on sexual behavior is accompanied by emesis. Reference '606 does not explicitly or implicitly teach the use of agonists selective for the D4 dopamine receptor to treat sexual dysfunction.

Applicants respectfully submit that it is improper to combine the teachings of references '094 and '010, in addition to reference '606, with the teachings of the primary references to obtain the compounds of the present invention.

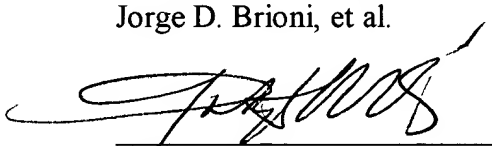
For all the above reasons, and in view of the new set of claims submitted with the present reply, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-6, 8, 9, 11, 12, 14-23, 25-27 and 29 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the new set of claims and the aforementioned remarks, Applicants respectfully believe that the application is in condition for allowance and respectfully request that the Examiner withdraw all outstanding rejections.

Should the Examiner have any concerns regarding the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,
Jorge D. Brioni, et al.



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